Continuous-flow step-economical synthesis of thiuram disulfides via visible-light photocatalytic aerobic oxidation†

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A continuous-flow photocatalytic synthesis of the industrially important thiuram disulfides has been developed, utilizing O2 as the oxidant and Eosin Y as the photoredox catalyst. This highly atom- and step-economical method features much reduced reaction time as well as excellent product yield and purity, making it a sustainable and potentially scalable process for industrial production.

The vulcanization accelerator is indispensable to the rubber industry and plays a critical role in rubber processing,1 as it improves rubber performance and prolongs the service life. Currently, the most popular classes of vulcanization accelerators include thiazole, sulphonamide, thiuram, dithiocarbamate and ammonia. Thiuram has garnered much attention due to its excellent vulcanization activity and high degree of vulcanization,1,2 and has become a mainstream vulcanization accelerator. Tetraethylthiuram disulfide (TETD, Scheme 1) is one of the most widely used thiuram-type accelerators. In recent years, the total annual output of TETD has seen a steady increase worldwide. Interestingly, it has also been reported to have diverse biological activities for treating alcoholism, cancer, HIV and diseases in seeds3 that range from the µm to mm levels. The small reactor scale allows for a much enhanced surface-to-volume ratio,23 which is particularly advantageous to heat and mass transfer thus offering much improved safety and reaction rate.26–28 In addition, microreactors can efficiently minimize the gap between the laboratory and pilot scale experiments, with a low scale-up effect than batch reactions. In particular, microflow technology reduces the cost by not requiring airtight equipment for gas–liquid reactions.29

However, a small reactor diameter poses the problem of handling solid formation from reagents, products or catalysts, which leads to clogging events. For example, Luo’s group

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Scheme 1 Structure and applications of TETD (disulfiram)
reported a continuous-flow synthesis of TETD under conditions that employed \( \text{H}_2\text{O}_2 \) as the oxidant.\(^{43} \) The yield of TETD reached 93% within 3 min of residence time. However, the requirement of excess carbonic acid remains a problem, and the resulting sodium carbonate could clog the microchannel. Thus, we aimed to develop a more economical and environmentally friendly continuous microflow approach to synthesize thiuram disulfides, in the hope of solving the above-mentioned challenges. Based on the reported solutions,\(^{30-32} \) a more attractive strategy would involve the introduction of a gas phase for increasing the overall flow rate in microchannels. The gas–liquid segments at a high flow rate cause enhanced turbulence, which can help flush out solids stuck to the channel wall. Molecular oxygen (\( \text{O}_2 \)) has received increasing attention from both academia and industry as the most readily available green oxidant on the planet.\(^{33} \) Monbaliu and coworkers reported the photocatalytic aerobic oxidation of 2-chloroethyl ethyl sulfide (CEES) with an \( \text{O}_2 \)-pressurized continuous-flow setup,\(^{34} \) and the yield of the corresponding product, 2-chloroethyl ethyl sulfoxide (CEESO), reached 98% in 4 min under the optimized conditions. Therefore, we envisioned a method without the use of toxic and stoichiometric oxidants by using \( \text{O}_2 \) or compressed air as a green oxidant. The rate of the biphasic reaction can be increased in the flow due to the improved mass transfer compared to the batch reaction. Moreover, quantitative consumption of gaseous reactants can be realized by using a mass-flow controller.\(^{35} \)

The envisioned synthesis of TETD is shown in Scheme 2. A photocatalyst was used to facilitate the oxidation.\(^{36} \) According to the Beer–Lambert law, the small size of the microchannel can greatly increase light absorbance of the catalyst.\(^{37,38} \) The proposed method employed a semi-equimolar ratio of diethylamine (1.0 equiv.) and carbon disulfide (1.1 equiv.) that forms dithiocarbamate in situ.\(^{33} \) According to market reports, thiuram accounts for a large proportion of vulcanization accelerators. However, safety and efficiency issues emerged as the scale went up in traditional production. In this work, the preparation of TETD in batch and continuous-flow modes was first investigated as a proof of principle. With the optimal conditions determined, the synthesis of other thiuram disulfides was then studied.

First, a set of photocatalysts was screened in the batch reaction with ethanol as the solvent under irradiation by a 13 W green LED. The results are shown in Table 1. Reactions using bromocresol green, bromocresol purple (sodium salts) and methylene blue gave unsatisfactory results since the yields were below 30%. To our delight, we found that the chromatographic yield of TETD could reach 98% when the sodium salt of Rose Bengal (RB) was employed as the photocatalyst. Eosin Y, a popular and versatile photocatalyst,\(^{39} \) does not work as well as RB with which 72% chromatographic yield was obtained. However, the limited solubility of RB in ethanol renders it inappropriate for flow synthesis since clogging of the microchannel was observed. Different light sources were evaluated, in which the yields of TETD under blue and white LED light were 60% and 48%. Therefore, the green LED was an optimal light source for Eosin Y-catalysed reactions.

Using Eosin Y as the optimal catalyst, we set out to explore the most important operational conditions in microflow. A microreactor system was dedicatedly designed for the continuous synthesis of TETD, which is shown in Fig. 1 and 2. Herein, the reaction solution was introduced into one of the two inlets of a T-micromixer using a plunger pump, which contained diethylamine and carbon disulfide premixed in a near-equimolar ratio of 1/1.1. The other inlet of the T-micromixer was connected to a computer-controlled mass-flow controller (MFC) attached to the oxygen tank. The retention time was adjusted by changing the flow rate of the MFC or pump. For the reactor section, the outlets of the T-micromixer were connected to the photoreaction microchannel (PTFE, diameter: 1/16\( ^\prime \)) surrounded by a 13 W green LED light strip. Segmented flow (Fig. 1b) gradually formed when oxygen gas and the solution phase converged in the T-micromixer. The gas–liquid flow pattern, often known as the Taylor flow,\(^{40} \) was expected to provide a much higher reaction rate than that by the batch approach, due to the enhanced contact area and pressure drop at the gas–liquid interface. A back-pressure regulator (BPR) was installed downstream to control the overall pressure of the system.

![Scheme 2 Reaction diagram of the step- and reagent-economical synthesis of TETD.](image)

**Table 1** Comparison of TETD yields (%) with different visible-light photocatalysts (the colors of bars represent the exact colors of catalysts)
With the flow system established, we first probed the pressure effect on the yield using ethanol as a green solvent. Fig. 3a shows that higher pressure led to improved TETD yield. A complete conversion could be achieved when the pressure was set to 0.5 MPa. Notably, solid precipitation was observed if the solution resided for a prolonged period of time in the microchannel at higher pressure. Therefore, 0.5 MPa was selected as the optimal pressure to avoid clogging.

The influence of residence time (t_R) was investigated next and was adjusted by changing the flow rates of the liquid and gas phases (Fig. 3b). A varying degree of pulse was observed at low flow rates due to the relatively large cavity volume of the adjustable, stainless steel BPR (approximately 3 mL, Fig. 4a), which increased the difficulty of precisely controlling the residence time of the gas–liquid segments. Thus, a BPR (manufactured by IDEX, Fig. 4b) with a small cavity volume (approximately 0.1 mL) was adopted. We monitored the time required for the pulsed gas–liquid segmented flow to reach the steady state, and found that the pulse effect diminished with an increasing flow rate. Fig. 3b shows the HPLC yields of TETD with ethanol as the solvent under different residence times. The yield increased with the residence time, which was prolonged not by reducing the flow rate, but by increasing the length of the microchannel under a constant flow rate to maintain a workable Taylor flow pattern (Fig. 4c). The reaction could be completed with a t_R of 25 min, which was significantly shortened compared to that of the batch reaction (3.5 h). The chromatographic yield reached 100%, and the TETD product was isolated in 94% yield. Next, we evaluated the potential for scale-up and obtained 11.24 g of TETD crystals produced by flow synthesis (left) and powders produced by conventional batch synthesis (right).
TETD with an isolated yield of 96%. Gratifyingly, crystalline TETD could be readily isolated by simply evaporating the solvent, probably due to the absence of the unreacted starting material and superstoichiometric amount of the oxidant. In contrast, most commercial TETD products manufactured by conventional processes are in powder form (Fig. 5).

Next, we turned our attention to another commonly-used solvent in industry, methanol. The advantages of using methanol include lower cost and energy-efficient post-production recycling due to its low boiling point. The applicability of methanol was explored under the same conditions as ethanol. Fig. 3c shows the HPLC yields of TETD with methanol as the solvent.

### Table 2: The scope of the photocatalytic synthesis of thiuram disulfides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>94&lt;sup&gt;a&lt;/sup&gt;, 90&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>2b</td>
<td>53&lt;sup&gt;c&lt;/sup&gt;, 43&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>2c</td>
<td>64&lt;sup&gt;a&lt;/sup&gt;, 69&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>2d</td>
<td>60&lt;sup&gt;a&lt;/sup&gt;, 72&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>2e</td>
<td>39&lt;sup&gt;a&lt;/sup&gt;, 46&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>2f</td>
<td>66&lt;sup&gt;b&lt;/sup&gt;, 76&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>2g</td>
<td>64&lt;sup&gt;e&lt;/sup&gt;, 34&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>1h</td>
<td>2h</td>
<td>61&lt;sup&gt;e&lt;/sup&gt;, 52&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>1i</td>
<td>2i</td>
<td>12&lt;sup&gt;a&lt;/sup&gt;, 15&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>1j</td>
<td>2j</td>
<td>9&lt;sup&gt;e&lt;/sup&gt;, 21&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
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<sup>a</sup> Unless otherwise indicated, the reaction conditions were as follows: photo-flow microreactor, molar ratio of 1:CS₂: Eosin Y = 1: 1: 1: 0.002, pressure = 0.5 MPa, residence time = 25 min, 13 W green LED light, oxygen, EtOH (as the default solvent).  <sup>b</sup> Residence time = 20 min, MeOH as solvent.  <sup>c</sup> Residence time = 5 min.  <sup>d</sup> Residence time = 6.5 min, MeOH as solvent.  <sup>e</sup> Batch, pressure = 0.1 MPa, reaction time = 3.5 h.  <sup>f</sup> Batch, pressure = 0.1 MPa, reaction time = 3.5 h, MeOH as solvent.
with different residence times. When $t_R$ was set to 20 min, the chromatographic yield was the maximal (100%), greater than that with ethanol. In other words, methanol ensures a shorter reaction time than ethanol with the same level of yield. However, the yield started to decrease with longer residence times, which was probably attributed to the observed clogging of the microchannel by the product at low flow rates.

With the success of the flow synthesis of TETD, we attempted to test the scope of this method (Table 2). The same experimental conditions as that for TETD were employed to prepare other thiuram disulfides in flow. It is worth mentioning that the low solubility of tetramethylthiuram disulfide (2b) in both methanol and ethanol resulted in a gradual deposition of the solid product inside the microchannel which eventually led to a total blockage. Therefore, we had to increase the flow rate to flush out the deposited solid, at the cost of lower yield due to reduced residence time. When methanol was used as the solvent, the isolated yield reached up to 43% with a $t_R$ of 6.5 min (see the ESI†). When ethanol was used, a slightly higher yield of 53% could be achieved with a $t_R$ of 5 min. The corresponding products were obtained in good yields as n-propyl and n-butyl analogs (2c and 2d). Diisobutylamine was treated with CS$_2$ to give 2e in moderate yields both in ethanol and methanol. For 2f–2h, it is noteworthy that they are much less soluble than other thiuram disulfides, and exhibit high viscosity in the crude form, which made them unsuitable for the flow reactor. A microreactor with a larger diameter might be helpful, but is unlikely to completely solve the clogging problem due to the extra low solubility of 2f–2h in most organic solvents. Instead, we carried out the photocatalytic synthesis in batch mode. To our delight, the isolated yields were satisfactory with a reaction time of 3.5 h (entries 6–8). It was later found that dipentamethylenethiuram disulfide (2f) has higher solubility in methanol, and therefore the flow reaction was also performed with an isolated yield of 66%. In contrast, 2i and 2j were obtained in poor isolated yields as aromatic secondary amines are less reactive. The melting ranges of the isolated TETD, TMTD and TBzTD were 66–68 °C, 142–144 °C and 98–100 °C, respectively, which were identical to those of commercial samples manufactured by the conventional process in the rubber industry. NMR, FT-IR and MS analyses also indicated that they were identical to the commercial products (see the ESI†).

A plausible mechanism of this photocatalytic transformation is proposed in Scheme 3. Firstly, diethylamine and carbon disulfide undergo an addition reaction to form diethyl-dithiocarbamic acid in situ. Exposure of Eosin Y (EY) to visible-light promotes EY to its excited state (EY$^*$). Subsequently, diethyl-dithiocarbamic acid loses an electron to generate a thiyl radical via proton-coupled electron-transfer (PCET). Then, single-electron oxidation of [Eosin Y]$^+$ by O$_2$ forms the superoxide radical (O$_2^-$) and closes the photoredox cycle. Finally, the thiyl radical reacts with the diethyl-dithiocarbamate anion to give the desired thiuram disulfide product.

Additional experiments were carried out to verify the possibility of singlet oxygen in this photochemical process. Diphenylisobenzofuran (DPBF), a singlet oxygen trapping agent, can react with $^1$O$_2$ to form the corresponding endoperoxide (DPBF-EP) and eventually $\alpha$-benzoylbenzophenone (Scheme 4). The UV-Vis spectra of a mixture of Eosin Y and DPBF under irradiation by a green LED light displayed a sharp decrease in the absorption intensity at around 409 nm (Fig. 6). These results suggested that $^1$O$_2$ was involved as the reactive oxidative species in the reaction.

Scheme 3 A plausible mechanism for the aerobic photocatalytic synthesis of thiuram disulfide.

Scheme 4 The singlet oxygen trapping reaction of DPBF.

**Fig. 6** UV-Vis spectra of the reaction mixture with 1 h intervals between readings (the characteristic absorption of DPBF is at 409 nm). Reaction conditions: Batch, molar ratio of DPBF : Eosin Y = 1 : 1, O$_2$ pressure = 0.1 MPa, green LED light, and EtOH as solvent.
Conclusions

In conclusion, we have developed a mild and highly efficient visible-light photocatalytic aerobic oxidation reaction in continuous flow to access thiuram disulfides. This operationally simple method circumvents the drawbacks of using strong acids/bases and hazardous oxidants in conventional synthesis. It is advantageous with a green oxidant and solvent, short reaction time, low catalyst loading, much improved purity and high yield. We expect this metal-free continuous-flow process to serve as a scalable and sustainable process for manufacturing thiuram disulfides and other important sulfur-containing industrial products.

Conflicts of interest

The authors received research funding from Hebi Uhoo New Materials Co., Ltd for this study. Hebi Uhoo New Materials Co., Ltd and Nanjing University have jointly filed a patent for the continuous-flow synthesis of thiuram disulfides via photocatalysis (Application# 202011315319.5).

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Notes and references